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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2016/2017

Carlos César da Fonte Senra

Terapias Minimamente Invasivas da Artrose do Joelho

Minimally Invasive Therapies of Knee Osteoarthritis

março, 2017

Carlos César da Fonte Senra

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Mestrado Integrado em Medicina

Área: Medicina

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Doutor Carlos Vaz

Trabalho organizado de acordo com as normas da revista:

Acta Reumatológica Portuguesa

março, 2017

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Carlos César da Fonte Lema

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
201108625	20 / 03 / 2017

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Minimally Invasive Therapies of Knee Osteoarthritis

ORIENTADOR

Doutor Carlos Vaz

COORIENTADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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Aos meus pais, à minha irmã, aos meus avós,

aos meus amigos e colegas

Minimally Invasive Therapies of Knee Osteoarthritis

Abstract

Knee osteoarthritis (OA) is a very common disease and a leading cause of disability. As the knee is an easy-accessible joint, local intraarticular therapies are raising interest as new medications and medical devices are available for injections, since it can avoid the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and surgery. Our review explores the clinically-evidence effective and minimally invasive treatment options available for knee OA management. The search strategy for this literature review was conducted by using the key words “knee osteoarthritis” and “intraarticular” and “therapeutics” in the PUBMED database. Among the literature, the effectiveness of Hyaluronic acid (HA) is controversial. The different molecular mass available has some responsibility in this issue. HA formulations with higher molecular mass present consistently more positive results in a long time management. Corticosteroids injections are effective in acute knee pain and effusion, without long time effect, though. Platelet-rich plasma have shown positive results among all the literature reviewed, with long time effects and disease modifying properties related to its growth factors that promote tissue healing and regeneration. A variety of novel therapies have been developed in recent years. Among them, mesenchymal stem cells injection is a promising regenerative treatment which has shown positive results in two recent randomized controlled trials, and it was considered as effective as hyaluronic acid. Genetic therapies using transduced chondrocytes expressing TGF-beta also presented promising results in two randomized trials. Polynucleotides injections also showed similar results with HA. Other single studies were found and are explored in our paper.

Introduction

Knee osteoarthritis (OA) is a very common disease that affects approximately 250 million people worldwide and is one leading cause of global disability[1]. The standard recommendations of knee OA management consist of nonpharmacological approaches (such as weight loss, exercise and braces), followed by analgesic medication, including nonsteroidal anti-inflammatory drugs (NSAIDs) and lastly surgery[2]. A recent study has suggested that surgical treatment results in greater pain relief and functional improvement compared to nonsurgical treatment, however more serious adverse events are reported in surgical treatment[3]. As knee is an easy-accessible joint, intraarticular therapies have an inherent appeal as it mitigates some systemic effects of NSAIDs, including gastrointestinal bleeding and myocardial infarction, and avoid adverse events of surgical treatment[4]. The purpose of our study is to evaluate minimally invasive and clinically-evidence based therapies that can be offered to those patients in which NSAIDs failed to relief pain and improve function, NSAIDs are contraindicated and are not indicated for surgery.

Methods

A search was conducted at PUBMED up to October 2016 using the key words “knee osteoarthritis” AND “intraarticular” AND “therapeutics”. Studies published prior to 2006, that involved animal experience, were related to surgical procedures/arthroscopy or that were not in English or Portuguese were excluded. An abstract quality assessment was performed by both authors to exclude low quality studies or others not related with the aim of the study.

Results

Hyaluronic Acid ("Viscossuplementation")

Hyaluronate is a natural component of synovial fluid, acting as a joint lubricant and shock absorber. It has a molecular mass ranching from 6500 to 10900 kDa in a normal synovial fluid, however in knee OA hyaluronate is depolymerized (molecular mass 2700 to 4500 kDa) and is cleared at higher rates[4].

17 studies were found using our inclusion/exclusion criteria evaluating clinical evidence to use hyaluronic acid (HA) injections in knee OA: 12 clinical trials (Table I) and 5 systematic reviews/meta-analysis. Among 7 randomized-controlled trials (RCT) accessed, 5 showed superiority of HA injections in pain relief and joint function[5-9], whereas 2 showed no statistically significant difference compared to placebo[10,11]. A meta-analysis conducted by Bannuru *et al*. evaluating 5 trials with 712 patients with knee OA suggested equal efficacy of HA injections compared to oral NSAIDs in terms of pain, function and stiffness with a better safety profile for the first option[12]. In addition, three reviews concluded that HA injections could be a safe and efficacious option for knee osteoarthritis treatment[13-15]. On the other hand, a meta-analysis conducted by Rutjes *et al.* analysing 89 trials involving 12667 participants concluded that HA injections have a small and clinically irrelevant benefit in terms of pain management in knee OA[16].

Table I – Clinical trials evaluating hyaluronic acid in knee osteoarthritis

Author/year	Study design	Conclusions
Waddell *et al.* 2015 [17]	Retrospective; 50 patients requiring aspiration at the time of viscossuplementation compared with 50 matched patients without effusion	Effusion requiring aspiration at the time of hyaluronic acid injection does not negatively impact outcome
Van der Weegen *et al.* 2015 [10]	RCT with 196 patients with knee OA comparing HA sodium hyaluronate with saline injections; 6 months follow-up	3 weekly injections of HA (sodium hyaluronate) were not superior to saline in 6 months follow-up
Petrella, R. J. *et al.* 2015 [18]	RCT with 98 patients with knee OA comparing Hydros, Hydros-TA and cross-linked HA single injections; 26 weeks follow-up	Single injection of Hydros and Hydros-TA is effective in pain relief compared to active control; hydros-TA has a faster effect
Leighton, R. *et al.* 2014 [19]	RCT with 442 patients with knee OA comparing NASHA with methylprednisolone single injection; 12 weeks follow-up	Single injection NASHA was not inferior to methylprednisolone at 12 weeks in pain score (WOMAC)

Ishijima M. *et al.* 2014 [20]	RCT with 200 patients with knee OA comparing HA injections with oral NSAID; 5 weeks follow-up	The efficacy of HA injections is not inferior to that of NSAIDs and is a more safe treatment
Arden, N. K. *et al.* 2014 [5]	RCT with 218 patients with knee OA comparing NASHA with saline injections; 6 weeks follow-up	NASHA injections has a significant pain improvement at 6 weeks follow-up among patients without effusion at baseline
Strand, V. *et al.* 2012 [6]	RCT with 319 patients with knee OA comparing Gel-200 with saline single injection; 13 weeks follow-up	A single injection of Gel-200 is effective and well tolerated relieving pain over 13 weeks
Navarro-Sarabia, F. *et al*. 2011 [7]	RCT with 306 patients with knee OA comparing cycles of HA with saline injections; 40 months follow-up	Repeated cycles of HA injections improve pain and function in-between cycles and this beneficial carry-on for a year after the last cycle
Jorgensen, A. *et al*. 2010 [11]	RCT with 337 patients with knee OA comparing HA sodium hyaluronate with saline weekly injections for 5 weeks; 1 year follow-up	Five injections of HA (sodium hyaluronate - Hyalgan®) did not improve pain, function and analgesic consumption over 3,6,9 and 12 months follow-up
Chevalier, X. *et al.* 2010 [8]	RCT with 253 patients with knee OA comparing Hylan G-F 20 with saline single injection; 26 weeks follow-up	Single injection hylan G-F 20 is safe and statistically significant in pain relief versus placebo
Altman, R. D. *et al.* 2009 [9]	RCT with 588 patients with knee OA comparing HA (1% sodium hyaluronate) with placebo; 26 weeks follow-up	Three weekly injection of HA (1% sodium hyaluronate) resulted in significant pain relief and joint function over a 26 weeks follow-up
Lundsgaard, C. *et al.* 2008 [21]	RCT with 251 patients to receive four weekly HA sodium hyaluronate (Hyalgan®), saline 20 ml (distension) or saline 2ml (placebo); 26 weeks follow-up	No difference between groups reducing knee pain

RCT: Randomized controlled trial; HA: hyaluronic acid; NSAID: non-steroidal anti-inflammatory drug; NASHA: cross-linked (high molecular wheight) HA formulation; Gel-200: cross-linked (high molecular wheight) HA formulation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; Hydros: cross-linked (high molecular wheight) HA formulation; Hydros-TA: hydros plus 10 mg triancinolone; Hylan G-F 20: high molecular wheight (mean 6000 kDa) HA formulation;

Corticosteroids

Corticosteroids (CS) injections provides pain relief and local anti-inflammatory effect by the prostaglandin synthesis inhibition and decreasing collagenases activity. A total of 5 studies investigating the efficacy of CS injections were found. One RCT and one retrospective pilot study demonstrated that CS injections are effective in pain reduction and in functional improvement, being essential prior joint aspiration[22,23]. CS injections are also more suitable for relieving pain in a short-time basis, with a better efficacy compared to viscossuplementation in the first 4 weeks[24]. Another study using a different approach concluded that adding triamcinolone to hyaluronic acid improves first-

week symptoms[25]. A RCT conducted by Bodick *et al*. reported that an extended-release formulation of triamcinolone prolongs and improve pain relief compared to standard immediate-release triamcinolone[26].

Platelet-rich plasma (PRP)

Eleven studies evaluating the clinical-evidence of intraarticular platelet-rich plasma (PRP) in knee OA were found: four RCT (table II), five non-randomized trials and two meta-analysis. All RCT showed that PRP injections are an effective treatment for moderate grade knee OA (level 1 of evidence in all studies)[27-30], despite the different PRP formulations used. Four non-randomized, single-arm, studies, with a total of 567 patients receiving PRP injections concluded PRP to be effective in pain reduction and function improvement[31-34]. A non-randomized trial conducted by Kon *et al*.[35] demonstrated that PRP is more effective reducing pain and symptoms than HA injections. A recent meta-analyse conducted by Laudy *et al.*[36] with ten trials comparing PRP injections with placebo revealed PRP more effective in pain reduction and function improvement at 6 months post-injection. Another meta-analyse reached the same results with PRP being an effective treatment for pain reduction compared with pre-treatment condition[37]. Several studies revealed PRP injection being more effective in younger patients with low degree of articular degeneration[30,31,33,35,37].

Table II – Randomized Controlled Trials evaluating platelets-rich plasm in knee osteoarthritis

Author/year	Study design	Conclusions
Filardo, G. *et al.* 2015 [27]	RCT, with 192 patients with knee OA comparing PRP with HA injections; 12 months follow-up	Both treatments are equal effective improving function and reducing symptoms
Vaquerizo, V. *et al.* 2013 [28]	RCT, with 96 patients with knee OA comparing PRGF with HA injections; 48 weeks follow-up	PRGF proved to be better than HA injections in terms of pain reduction and functional improvement
Sanchez, M. *et al.* 2012 [29]	RCT, with 176 patients with knee OA comparing PRGF with HA injections; 24 weeks follow-up	PRGF showed better short-term results compared to HA injections in symptoms relief
Cerza, F. *et al.* 2012 [30]	RCT, with 120 patients with knee OA comparing ACP with HA injections; 24 weeks follow-up	Treatment with ACP showed a better clinical outcome compared to HA injections

RCT: randomized controlled trial; OA: osteoarthritis; HA: hyaluronic acid; PRP: platelets-rich plasma; PRGF: platelets rich in growth factors (a specific PRP formulation); ACP: autologus conditioned plasma (a specific PRP formulation).

Novel therapies

A variety of new intraarticular therapeutics has been attempted in knee OA. Our research found four recent papers related to Mesenchymal Stem Cell (MSC) therapies. A RCT with 424 patients with knee OA evaluated the relationship between cell concentration in bone marrow aspiration (without MSC isolation and expansion) and pain management, concluding that higher cell count ($>4\times10^8$) is associated with a better outcome[38]. Another RCT comparing a single injection of allogenic bone marrow mesenchymal stem cells with HA in 30 randomized patients with knee OA concluded that it significantly improved cartilage quality and might be a valid alternative for pain management, lacking logistically inconveniences of autologous MSC treatment[39]. Two phase one studies evaluating autologous adipose tissue derived MSC in knee OA patients suggested it might be a safe and promising treatment modality for these patients[40,41].

A RCT conducted by Lee *et al.*[42] evaluated the efficacy of a single injection of a 1:3 mixture of genetically manipulated chondrocytes to express TGF-β1 and normal allogenic human chondrocytes against placebo in 54 patients with knee OA concluding that in 24 weeks follow-up active treatment resulted in significantly pain and function improvement. Notwithstanding, an anaphylactic reaction to the preservation medium was reported in one patient.

Two RCT evaluating the efficacy of intraarticular injections of polynucleotides compared to HA injections in a total of 135 randomized patients with knee OA showed similar results of both treatments in pain reduction[43,44].

A single RCT evaluated the effect of intra-articular injections of a mixture of sodium bicarbonate with a single or double dose of calcium gluconate concluding that this treatment is effective in reducing symptoms associated with OA. A higher dose of calcium gluconate is associated with further joint-space narrowing prevention. The positive effect of bicarbonate is attributed to its alkalinity whereas calcium gluconate avoid hyperosmotic conditions in extracellular matrix by allowing the linkage between chondrocytes and bone proteins[45]. Another RCT attempted 4 weekly intra-articular injection of a bisphosphonate (clodronate) resulting in a small and transient benefit over a 12 weeks follow-up compared to placebo[46]. A recent prospective study found etanercept

(Tumor necrosis factor-alpha inhibitor) injections being more effective in pain management than high molecular weight HA in knee OA patients[47].

Discussion

Intra-articular HA injections in knee osteoarthritis treatment are still a controversial issue due to the contradictory results obtained from different clinical trials. Of note, two RCT that showed no difference between HA injections and placebo used a hyaluronic acid formulation with a low molecular mass (sodium hyaluronate, Hyalgan® 500 to 730 kDa)[11] and medium molecular mass (2200 kDa)[10], respectively. Another RCT that reported no difference between HA injections, saline distension and placebo used a HA formulation with a low molecular mass (Hyalgan®)[21]. On the other hand, all studies that used hyaluronic acid formulation with a high molecular mass (mean 6000 kDa) found positive effects in knee OA[5,6,8,18-20]. Therefore, molecular weight could represent a major issue in viscossuplementation. Previous studies had already suggested superiority of high molecular mass formulation of HA[48] and this could explain the incongruent results from several systematic reviews and meta-analysis that do not differentiate HA formulations. An effusion at baseline do not affect HA effects if we aspire it previously[5,8,17].

CS injections remains among the literature reviewed an efficacious option to improve joint pain and function in a short-period and fast-acting basis, so far[22,24,25]. Some studies reinforce this short-acting improvement with no efficacy of CS injections against placebo over 12 weeks follow-up, though[49]. There is not consensus regarding which CS use, doses and frequency of injection, being still a individually tailor selection[50].

PRP is an autologous blood product with a high content of growth factors stored in alpha-granules of platelets and a low content of white blood cells (WBC), which is raising interest among physicians[36]. There are different PRP formulations with variable concentrations of growth factors and WBC[33]. This variability could affect the studies outcomes since a high content of WBC, which release proinflamatory cytokines, are associated with increased pain and swelling[51,52]. Our review were consistent with a positive effect of PRP injections in pain reduction and function improvement in knee OA. The RCTs reviewed all compared PRP with HA injections [27-30]. Filardo *et al*.[27] concluded PRP and HA injections being equal efficacious in knee OA, interestingly, the other three RCT that had positive results for PRP injections compared to HA injections used PRP formulations (Platelets rich in growth factor[28,29] and autologous conditioned plasma[30]) with a higher content of growth factors and a lower content of WBC. These results put in perspective the importance of PRP formulations and cell/cytokines concentration in the

final outcome. More studies are needed in this field to better understand which PRP formulation is the most effective.

MSCs therapy is a promising treatment in knee OA since those are multipotent cells with capacity to differentiate in different cellular lines of mesodermal origin including cartilage, ligaments and tendon[38]. MSC could be autologous: bone marrow derived or adipose tissue derived with inconvenient related to the invasive bone marrow aspirations and adipose tissue extraction and also, MSC isolation and cell culture not suitable for an outpatient setting. In alternative other authors instead of isolating MSC, use bone marrow concentrates containing a fraction of MSC and other bone marrow cells (including hematopoietic stem cells, monocyte precursor cells, macrophages, T cells, B cells and others) with comparable results without MSC being isolated, suggesting that other bone marrow cells could affect tissue healing[38]. Adipose-derived MSC are a promising alternative of autologous MSC therapies but further RCT studies are needed to access efficacy[41]. Allogeneic MSC are a cheaper and more convenient way for MSC intraarticular therapies. Despite the possibility of host immune rejection, MSC are *immune evasive* and inhibit immune responses. A RCT with 15 patients receiving allogenic MSC reported no safety concerns[39]. In spite of the potential of allogeneic MSC, larger RCT are needed to evaluate safety profile.

Genetically manipulated chondrocytes expressing TGF-β are a recent treatment modality for knee OA. TGF-β is thought to have regenerative, anti-inflammatory and immunosuppressive properties, stimulating proteoglycan synthesis and growth of articular chondrocytes. This cell-mediated gene therapy consist of a mixture of transduced allogenic chondrocytes overexpressing TGF- β and normal allogenic chondrocytes. Non-transduced chondrocytes are included to fill cartilage defects and act as an additional target for TGF-β signalling[53]. This therapy had promising results in a RCT and a phase two study, being sufficient for further clinical testing[42,53].

Intraarticular polynucleotides act as a 3D gel with a high content of water with mechanical effects in joint lubrication and moisturizing. In addition, polynucleotides provide synovial fluid with nucleotides, nucleosides, purine and pyrimidine that can therefore support the physiological repair processes of cartilage. Two RCT showed similar results of intraarticular polynucleotides compared to HA injections, being an alternative for this last treatment [43,44].

Intra-articular etanercept had promising results in knee OA pain management, suggesting TNF-α is one factor that induces OA pain. However, one single trial was found and more studies are needed to evaluate efficacy and safety [47].

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Agradecimentos

Ao Professor Doutor Carlos Vaz pela sua orientação, total apoio, disponibilidade, pelo saber que transmitiu, pelas opiniões e críticas, total colaboração no solucionar de problemas e dúvidas e por todas as palavras de incentivo.

À minha irmã, pela revisão linguística.

Aos meus colegas e amigos por todo o apoio e incentivo.

Acta Reumatológica Portuguesa

Normas de publicação

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A Acta Reumatológica Portuguesa (ARP) é uma publicação científica internacional, revista por pares, abrangendo aspectos clínicos e experimentais das doenças reumáticas. São publicados artigos originais, artigos de revisão, casos clínicos, imagens em Reumatologia, cartas ao editor e artigos que visam melhorar a Prática Clínica (recomendações e protocolos clínicos, por exemplo).

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Direcção-Geral da Saúde – Divisão de Doenças Transmissíveis, Março de 2005.

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Agradecimentos

Incluir nesta secção agradecimentos a pessoas que tenham contribuído para o trabalho mas sem autoria. Instituições ou fontes de apoio financeiro também poderão aqui ser indicadas.

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